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Article (Accepted Version)

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The Regulation of Clinical Stem Cell Research and Applications: three dynamics of global regulatory diversification

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The evolving regulatory landscape for clinical stem cell research is characterized by a conflict between the striving for international harmonization and an increasing process of global regulatory diversification.[1] Attempts of regulatory harmonization are exemplified, for instance, by the 2016 Guidelines for Stem Cell Research and Clinical Translation by the International Society for Stem Cell Research (ISSCR 2016), the Advanced Therapy and Medicinal Products (ATMP) Regulation of the European Medicines Agency (EMA), or by the ATMP Cluster of the US Food and Drug Administration (FDA), EMA and Health Canada (Arcidiacono 2012). These processes of harmonization have evolved from a pharmaceutical model of drug development and the ideal of Evidence-Based Medicine (EBM), with the multiphase randomized controlled trial (RCT) system as methodological gold standard. In parallel to these developments, however, discontent with the use of the multi-phase trial system for the clinical validation of stem cell-based medicinal product has grown. A politics of opposition has emerged that has called for the use of alternative methods and forms of evidence, to reduce the costs of clinical testing and to increase access to non-systematically proven innovative interventions at an earlier stage. Calls for international harmonization in the stem cell field have been undermined too, by practical challenges to standardize clinical and cell processing procedures in large-scale, multi-country trials, which require a complex logistical infrastructure and significant financial resources. For academic researchers and small to mid-size biotech companies these resources are often not available (Rosemann 2014). Since industry involvement in stem cell medicine has remained at a low level, the mobilization of resources to take investigational stem cell products or therapies

[1] Parts of this contribution have been previously published in: Rosemann A, Bortz G, Vasen F, Sleeboom-Faulkner M. Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations. Regenerative Medicine. 11(7): 647-57 (2016). Material from that article is reprinted with permission of Future Medicine.

through rigorous multi-phase trials, remains typically a challenge. This politics of alter-standardization has taken an increasingly global form. Many impulses for regulatory change and a shift away from multi-phase trials for stem cell-based treatments, have come from Asia, especially from Japan, India, China and South Korea (Sleeboom-Faulkner et al. 2016). But opposition to EBM and the multi-phase trial system, and calls for the emerging of new models and methodologies of clinical innovation in the stem cell field has also increasingly evolved in the European Union and the USA. These clashes have resulted in three central dynamics of regulatory diversification. These developments challenge the use of multi-phase trial methodology as the central methodological instrument for therapy development in the stem cell field in many respects.

The emerging of a growing number of regulatory exceptions and exemptions

A first dynamic is the emerging of a growing number of regulatory exceptions and exemptions, which have been introduced by regulatory authorities in high-income countries, especially in the European Union and the USA (Faulkner 2016, Knoepfler 2014). Examples from the European Union are the "hospital exemption scheme", which has evolved as part of the EMA ATMP regulation, the "conditional approval scheme" and the "compassionate use program". The "hospital exemption scheme", as has widely been documented, allows for the provision of cellular therapies and medicinal products to individual patients "under the exclusive professional responsibility of a doctor" (source). According to Salter, Zhou and Datta, this scheme has provided "the opportunity for a legal market of authorized stem cell therapy products to emerge within the province of the clinical professionalism" (Salter, Zhou and Datta 2014: 359). The "conditional approval scheme", on the other hand, allows for market approval of a medicinal product at a later stage of a phase III trial, when data collection for efficacy and safety has almost been completed (Faulkner 2016). Compassionate use" program, in turn, allows access to medicinal products outside of phase III premarket clinical trials (Mittra et al. 2015). The "conditional approval scheme" and the "compassionate use program" are both part of EMA's pharmaceutical products regulation, but can also be applied to stem cell-based medicinal products (Faulkner 2016). While the hospital exemption scheme is unique to the European Union, the US FDA has introduced a range of similar regulatory

exceptions that aim (i) to speed up the transition from preclinical to clinical testing (the FDA "fast track approval" scheme), (ii) to realize more rapid authorization of phase I and II clinical trials, especially for trials that involve seriously ill patients with low life expectancy (the "accelerated approval" scheme), and (iii) to provide access to investigational new treatments parallel to FDA-approved phase II and III clinical trials ("compassionate use program") (Knoepfler 2014). The 21st Century Cure Act, that was approved by the US Congress in December 2016, has introduced additional options to accelerate market approval of new medicines, by offering possibilities to avoid going through rigorous, large-scale phase III trials (Kesselheim and Avorn 2016) and by promoting methodological alternatives to the multi-phase trial system such as adaptive and other new trial designs (Butler and Valentine 2016). What this growing number of regulatory exceptions and exemptions share is, that they either allow to shortcut the clinical trial process, or in some cases, permit possibilities for clinical innovation and sometimes commercial clinical applications outside of the multiphase trial system, but still within the confines and review procedures of national regulatory agencies. Another development in the USA has been a growing number of "right-to-try" legislation, which offer patients and physicians the choice to use not-yet approved investigational drugs (including cellular medicines) entirely outside of the regulatory control of the FDA (Bianco and Sipp, 2014; Darrow et al., 2015). These right-to-try laws have now been issued in more than 30 US states (Feibel 2017).

The flexible enforcement of regulatory standards

A second process of regulatory diversification is the flexible enforcement of regulatory rules in some countries, that enables the continued provision of experimental for-profit interventions with stem cells outside of the review and control structures of regulatory agencies. This has happened for various years in India and China, where governments responded only gradually to a flourishing grey-area market of stem cell therapies (Sleeboom-Faulkner and Patra 2011; Sleeboom-Faulkner et al. 2016; Sleeboom-Faulkner 2016). Unapproved for-profit therapies continue to be tolerated in these countries also after the introduction of national regulatory frameworks, which formally prohibit stem cell interventions outside of formally approved clinical trials. In China, the 2015 *Regulation for Clinical Stem Cell Research* has explicitly stated that the clinical translation of stem cell-based

approaches must occur through systematic clinical studies, which must follow from sound pre-clinical evidence (Rosemann and Sleeboom-Faulkner 2016). The core of this regulation is that stem cell trials can only be conducted in specifically authorized research hospitals and that for-profit applications of experimental stem cell interventions are legally prohibited (*ibid*.). Also in India, the 2013 *Guidelines for Stem Cell Research* (and previously in 2007 the *Guidelines for Stem Cell Research and Therapy*) have formally prohibited the use of stem cells in human patients, except in the context clinical trials approved by India's health authorities (Viswanathan et al. 2013; Indian Council of Medical Research 2013). Despite these formal regulatory prohibitions, however, large private hospitals and medical corporations have continued to offer their services on the Internet in both countries. In China various private clinics and companies continue to advertise stem cell treatments on the world-wide-web, including on English language websites that aim to attract international patients. Also in India, numerous stem cell clinics have an online presence and advertize to stem cell-based interventions for a broader range of conditions.

However, the toleration of unapproved stem cell therapies has by no means been restricted to middle-income countries, but it could also be observed in the USA. In the USA, the FDA took for several years a surprisingly relaxed approach to clinics that have offered autologous stem cell interventions to patients, which have sprouted all over the country during the last 8-10 years. According to research conducted in 2015, there are at present more than 350 US private clinics and businesses offering direct-to-consumer stem cell interventions to medical consumers, which have not been authorized by the US FDA. These interventions did not only include autologous stem cell treatments, but also interventions with autologous stem cells from multiple sources, and at least one clinic claimed to offer even human embryonic stem cell-based interventions (Turner and Knoepfler 2016). With a growing number of right-to-try laws in the USA and recent regulatory changes introduced by the 21st Century Cures Act, and further changes announced by the current Trump government, this large number of clinics can be expected to expand rather than to be clamped down.

The abandoning of the multiphase trial system

A third process of regulatory diversification in the stem cell field is characterized by the complete abandoning of the multiphase trial EBM system. This has recently

happened in Japan and steps into this direction have with the 21st Century Cure Act also been initiated in the USA. In Japan, the Japanese regulators passed the *Regenerative Medicine Promotion Act* (RMP Act) in 2013 (Government of Japan 2013). This Act formed the beginning of a far-reaching regulatory reform. The RMP Act was followed by an amended Pharmaceuticals Affairs Law, which went into effect late 2014 (Government of Japan 2014). Under the amended PAL, the regulatory conditions for the clinical testing and use of stem cell-based medicinal interventions were significantly transformed (Azuma 2015). The amended law allowed for conditional, limited-term market approval of stem cell products after early-phase clinical trials. Conditional approval can occur after positive clinical data from as few as ten patients (Cyranoski 2013) provided these first-in-human trials demonstrate that the tested cell products are safe and 'likely to predict efficacy' (Sipp 2015). Once the Japanese Pharmaceuticals and Medical Devices Agency has provided conditional approval for a stem cell intervention, clinical trial sponsors have the possibility to seek conditional market approval for up to 7 years (ibid.). Clinical efficacy is then tested in this time period in the context of postmarketing procedures, which can but do not have to include rigorous, multiphase trials (source). According to Sipp (2015), this evolving regulatory model in Japan has dramatically relaxed the need to demonstrate the clinical utility of cellular products prior to marketing, and raises critical questions regarding the testing of safety and treatment efficacy. As Sipp has pointed out, with this new approach "Japan clearly hopes to compete and succeed in the race to build a regenerative medicine industry by flattening a few hurdles" (Sipp 2015: 355). It is not unlikely that other countries will follow the Japanese regulatory model, or at least create additional types of regulatory exceptions in which (conditional) market approval of stem cell therapies can be granted without preceding phase I–III trials. In fact, exactly this has now happened in the USA. The passing of the 21st Century Cure Act in December 2016 has introduced various steps into a post-RCT world in the stem cell field, and in other emerging areas of medicine research. As Kesselheim and Avorn have stated, advocates have praised the Act as a 'means of speeding drug development' and to decrease 'the cost and duration of drugs and devices development (Kesselheim and Avorn 2016). This has involved the provision of various provisions that have been designed to 'reduce the amount and rigor of clinical testing before new drugs and devices can be approved for use' (ibid.). These include the use of alternative, less rigorous forms of evidence, such as observational

data and self-reporting of "patient experience" that were previously deemed as too subjective and unacceptable in the context of FDA approval procedures (Butler and Valentine 2016; Kesselheim and Avorn 2016). Many of the regulatory changes introduced by the 21st Century Cure Act will also apply to stem cell treatments, but it remains to be seen how applications for specific types of stem cell-based interventions are handled in practice.

Conclusions

The regulatory changes and developments introduced in the previous sections represent a gradual shift away from a pharmaceutics-oriented model of drug developments, that was based on the EBM and multiphase RCT system, and that has shaped the regulation of stem cell research in its initial phase, at least in the context of the European Union and the USA, but also in many other countries (Rosemann et al. 2016). Alternative methods and forms of evidence are now step-wise accepted in many parts of the word and are likely to partly replace the multiphase trial model for the approval of stem cell-based interventions, as well as approval procedures in other evolving fields of medicine research. Whether this development will be to the ultimate benefit of patients, as many advocates of the 21st Century Cure Act in the USA (and advocates of similar changes in various other countries) have claimed, remains to be seen. Some would probably argue that it is not, and that the current politics of alter-standardization, which is shaped by powerful economic and political interests, does misuse the desire of patients for more affordable and more rapidly to access cures, by justifying potentially dubious research and irresponsible business practices. Others would possibly say that the growing acceptance of less rigorous standards and data do in fact increase health risks for patients as well as risks for potential forms of financial exploitation. This in turn, could undermine trust in science and medicine at a broader level. Still others would probably reason that many of the regulatory changes that have been introduced in this paper, diminish hard-won ethical and methodological achievements, which have aimed to safeguard patients from potential misuse by the medical profession. No matter where you stand in these debates, it seems safe to say that the line between the realization of new benefits and opportunities for patients and the emerging of new risks, dangers and injustices is thin. The regulatory changes described in this paper require for that reason long-term

monitoring, to obtain a clear idea of their implications for patients and health care systems.

Acknowledgements:

This article has benefited from research support provided by the ERC (283219) and the ESRC (ES/I018107/1).

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